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TOWNSEND and TOWNSEND and CREW LLP

By: Patricia Andrus

PATENT  
Atty. Docket No.: 020801-000920US

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of:

Ian MacLachlan, *et al.*

Application No.: 09/243,102

Filed: February 2, 1999

For: SYSTEMIC DELIVERY OF  
SERUM STABLE PLASMID LIPID  
PARTICLES FOR CANCER THERAPY

Examiner: J. Zara

Art Unit: 1635

Declaration of Ian MacLachlan Under 37  
C.F.R. §1.132

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

I, Ian MacLachlan, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true.

2. I hold a Ph.D. (1994) from the University of Alberta, and a Bachelor of Science (1988) from the University of Alberta. I am presently the Chief Scientific Officer for Protiva Biotherapeutics, Inc. (Burnaby, Canada).

My field of expertise is gene delivery and gene therapy. I have authored nineteen publications in the field of gene delivery technology, gene therapy, and molecular genetics, and am a member of the American Society of Gene Therapy and the Science Council of British Columbia, Health Technology Committee. A true copy of my *Curriculum Vitae* is attached hereto as Exhibit A.

3. The present invention is directed to methods of treating neoplasias in mammals by administration of serum stable lipid-nucleic acid particles with a nucleic acid portion that is fully encapsulated within the lipid portion. The administration of serum stable lipid-nucleic acid particles is by injection at an injection site that is distal to the neoplasia in the mammal. The nucleic acid may encode an expressible gene. The nucleic acid-lipid particle may contain a protonatable lipid.

4. I am a named inventor on the above-referenced patent application. I have read and am familiar with the contents of the subject patent application. I have also read the Office Actions received from the United States Patent and Trademark Office dated October 10, 2001 and April 10, 2000. It is my understanding that the Examiner is concerned that the claimed methods are not enabled by the specification. Specifically, the Examiner states that the specification is enabling for (1) methods comprising the administration of the nucleic acid encoding HSV-TK and ganciclovir, which nucleic acid is fully encapsulated in the lipid formulation(s) explicitly disclosed, and (2) increased stability of fully encapsulated nucleic acids in serum which are present in lipid-nucleic acid particles comprising formulations 1.1, 1.2, 1.3, 1.4, and 1.5. However, the Examiner alleges that the specification is not enabling for treatment of any neoplasm by distal administration of any expressible gene fully encapsulated within any lipid-nucleic acid particle. In making this allegation, the Examiner states that treatment effects are not necessarily provided by a nucleic acid merely because that nucleic acid has not been degraded by nucleases in the serum of an organism.

5. This declaration is provided to demonstrate that practice of the claimed methods is fully enabled by the specification. This declaration presents (1) experiments in which nucleic acids fully encapsulated in lipid formulations are expressed in cells upon transfection; (2) experiments in which lipid-nucleic acid particles inhibited tumor growth after administration to mice seeded subcutaneously, intradermally and intravenously with tumors; and (3) *in vitro* experiments in which lipid-nucleic acid complexes transfected into tumor cells confer increased sensitivity to prodrugs, *i.e.*, increased tumor cell death. These experiments which are also described in the specification were done under my supervision. The results unequivocally demonstrate that (1) nucleic acids encapsulated in the lipid-nucleic acid particles of the present invention are effectively expressed for treatment of neoplasia; (2) administration of the lipid-nucleic acid particles of the present invention is effective for treating neoplasia; and (3) transfection of tumor cells with lipid-nucleic acid particles leads to tumor cell sensitivity to prodrugs. One of skill in the art can therefore practice the claimed methods using information provided in the specification, together with methodology known to one of skill in the art, with at most, only routine experimentation.

6. The models used in carrying out the foregoing experiments are art-accepted models for (1) measuring transfection of cells with nucleic acids and (2) treating neoplasia. As demonstrated by the examples, the methods of the present invention are effective for treating neoplasms by distal administration of expressible genes fully encapsulated within the lipid-nucleic acid particles disclosed and claimed in the patent application.

7. The expression of nucleic acids administered in the lipid-nucleic acid particles of the present invention was determined in three separate sets of experiments, all of which are set forth in the specification.

The first set of experiments is described in Example 8 of the specification. Mice were injected intravenously on day zero with mouse Lewis lung carcinoma cells. On day ten, mice were injected with lipid-nucleic acid particles containing a plasmid encoding the luciferase gene linked to a CMV promoter. At various time points after plasmid injection, mice were sacrificed and their organs and tumors were assayed for luciferase activity. A time course of luciferase activity at distal tumor sites is shown in Figure 4 of the specification.

The second set of experiments is described in Example 9 of the specification. Mice were injected subcutaneously on day zero with human colon adenocarcinoma cells. On days eleven and seventeen, mice were injected with lipid-nucleic acid particles containing a plasmid encoding the luciferase gene linked to a CMV promoter. The mice were sacrificed and luciferase activity in their organs and tumors was assayed. Luciferase expression is shown in Figure 5 of the specification.

The third set of experiments is described in Example 10 of the specification. Mice were injected intraperitoneally on day zero with tumor cells. On day fourteen, the mice were injected with a lipid-nucleic acid particle containing a plasmid encoding HSV-TK. The mice were sacrificed 24 hours later and expression of HSV-TK was determined using *in situ* RNA-RNA hybridization. Detection of HSV-TK expression in peritoneal tumors is shown in Figures 6A and 6B of the specification.

These examples unequivocally establish that nucleic acids administered in the lipid-nucleic acid particles as claimed in the present invention are *actually* expressed.

8. The effect of lipid-nucleic acid particles containing HSV-TK on tumor growth was determined in seven separate sets of experiments, all of which are set forth in the specification.

The first set of experiments is described in Example 2 of the specification. Four groups of mice, A, B, C, and D, were seeded subcutaneously with B16 mouse melanoma cells and treated with a lipid-nucleic acid particle containing a vector encoding HSV-TK (C and D) or vector alone (A and B) once daily on day five and on every day

following. Groups B and D were treated with ganciclovir once daily on day five and on every day following. Mice of group D either did not develop tumors, or they developed tumors significantly more slowly than mice of control groups A, B, or C.

The second set of experiments is described in Example 6 of the specification. Mice were seeded intradermally on day zero with B16 control cells or B16 cells stably transfected with HSV-TK. The mice were treated with ganciclovir in a lipid formulation once every day beginning on day four and on every second day following. Intradermal tumors stably transfected with HSV-TK showed no measurable growth when treated systemically with ganciclovir.

The third set of experiments is described in Example 7 of the specification. Mice were seeded intravenously on day zero with B16 tumor cells stably expressing HSV-TK. The mice were treated with ganciclovir in a lipid formulation once every day beginning on day two and on the two days following. There was a significant reduction in both size and number of metastatic tumor modules.

The fourth set of experiments is described in Example 11 of the specification. Mice were seeded intradermally on day zero with fibrosarcoma tumor cells. On days 5, 7, 9, 11, and 13, empty lipid-nucleic acid particles or lipid-nucleic acid particles containing a nucleic acid encoding HSV-TK were intravenously administered to the mice. Beginning on day 5, mice were treated intraperitoneally with ganciclovir twice daily for twelve days. Mice were sacrificed and their tumor volume was measured. Mice treated with HSV-TK in lipid-nucleic acid particles and ganciclovir have greatly reduced tumor volumes compared to controls. The results are shown in Figure 9B of the specification.

The fifth set of experiments is described in Example 13 of the specification. Mice were seeded intradermally on day zero with fibrosarcoma cells. On days 5, 7, 9, 11, and 13, empty lipid-nucleic acid particles or lipid-nucleic acid particles containing a nucleic acid encoding HSV-TK were intravenously administered to the mice. Beginning on day 5, mice were treated intraperitoneally with ganciclovir twice daily for twelve days. Mice treated with HSV-TK in lipid-nucleic acid particles and

ganciclovir have greatly increased long term survival. The results are shown in Figure 10 of the specification.

The sixth set of experiments is described in Example 14 of the specification. Mice were seeded intradermally on day zero with colorectal tumor cells. On day 5 and every other day following for eight days, empty lipid-nucleic acid particles or lipid-nucleic acid particles containing a nucleic acid encoding HSV-TK were intravenously administered to the mice. Beginning on day 5 and every day following, mice were treated intraperitoneally with ganciclovir once daily. Mice were monitored for survival. If tumors developed, mice were sacrificed and the tumors were collected and weighed. Mice treated with HSV-TK in lipid-nucleic acid particles and ganciclovir either did not develop tumors or else developed tumors significantly more slowly than other mice. The results are shown in Figure 11 of the specification.

The seventh set of experiments is described in Example 15 of the specification. Mice were seeded intradermally on day zero with colorectal tumor cells. On day 5 and every other day following for eight days, empty lipid-nucleic acid particles or lipid-nucleic acid particles containing a nucleic acid encoding HSV-TK were intravenously administered to the mice. Beginning on day 5 and every day following, mice were treated intraperitoneally with lipid formulated ganciclovir once daily. Mice treated with HSV-TK in lipid-nucleic acid particles and lipid formulated ganciclovir exhibited a marked reduction in tumor growth rate. The results are shown in Figure 12 of the specification.

These examples unequivocally establish that administration of lipid-nucleic acid particles as claimed in the present invention is an effective treatment for neoplasia, *i.e.*, tumor size and growth rate are reduced significantly and long term survival is enhanced significantly.

9. Thus, the examples in the specification, which use art-accepted tumor models, demonstrate that administration of lipid-nucleic acid particles is effective for treatment of neoplasia. Specifically, administration of the lipid-nucleic acid particles

of the present invention inhibited or slowed growth of subcutaneously, intradermally, and intravenously seeded tumors.

10. In addition to the extensive examples in the specification showing that tumor growth is inhibited or reduced by administration of the lipid-nucleic acid particles of the present invention, the specification provides extensive guidance to one of skill in the art for practicing the claimed invention. In particular, the specification provides teachings as to suitable therapeutic nucleic acids for use in conjunction with the present invention (*see*, page 10, line 14 to page 14, line 3). Moreover, the specification provides teachings as to preparation of the lipid-nucleic acid particles of the present invention (*see*, page 14, line 25 to page 18, lines 31). Furthermore, the specification provides teachings regarding disease indications suitable for treatment using the lipid-nucleic acid particles of the present invention (*see*, page 19, line 28 to page 20, line 16). The specification also provides teachings regarding the administration of the lipid-nucleic acid particles (*see*, page 20, line 17 to page 22, line 20). Therefore, these teachings enable one of skill in the art to practice the invention as claimed, *without* undue experimentation.

11. In addition to the extensive examples in the specification showing that tumor growth is inhibited or reduced by administration of the lipid-nucleic acid particles of the present invention and the extensive guidance in the specification to one of skill in the art for practicing the claimed invention, results from continuing experiments demonstrate that genes other than those encoding HSV-TK are effective in inhibiting tumor growth. In particular, nucleic acids encoding the cytokine IL-12, the tumor suppressor protein, apoptin, the cytotoxin, *Pseudomonas* exotoxin, and the suicide enzymes purine nucleoside phosphorylase and cytosine deaminase have all been shown to be effective in inhibiting tumor cell growth when administered in lipid-nucleic acid particles.

12. Five additional sets of experiments, which again use art-accepted tumor models, demonstrate the efficacy of the lipid-nucleic acid particles of the present invention. These experiments, which were not described in the specification, were conducted under my supervision and are described below.

In the first set of experiments, three groups of mice were seeded intradermally with MCA-207 sarcoma cells and treated with a lipid-nucleic acid particle containing a vector encoding the cytokine, IL-12 or lipid-nucleic acid particle alone once every other day beginning on day six. Mice received a total of five lipid-nucleic acid particle treatments. Mice were monitored for tumor growth. Tumor growth was inhibited in mice treated with lipid-nucleic acid particles containing a vector encoding IL-12. A graphic illustration of the results is attached as Exhibit B.

In the second set of experiments, mice were seeded intradermally with CT26 colon carcinoma cells and treated with a lipid-nucleic acid particle containing a vector encoding the tumor suppressor protein, apoptin. Mice received a total of five lipid-nucleic acid particle treatments. Mice were monitored for tumor growth. Tumor growth was inhibited in mice treated with lipid-nucleic acid particles containing a vector encoding apoptin. A graphic illustration of the results is attached as Exhibit C.

In the third set of experiments, mice were seeded intradermally with CT26 colon carcinoma cells and treated with a lipid-nucleic acid particle containing a vector encoding the cytotoxin, *Pseudomonas* exotoxin or lipid-nucleic acid particle alone once every other day beginning on day six. Mice received a total of five lipid-nucleic acid particle treatments. Mice were monitored for tumor growth. Tumor growth was inhibited in mice treated with lipid-nucleic acid particles containing a vector encoding *Pseudomonas* exotoxin. A graphic illustration of the results is attached as Exhibit D.

In the fourth set of experiments, B16 melanoma cells were transfected with a nucleic acid encoding purine nucleoside phosphorylase (PNP) in a lipid-nucleic acid complex and exposed to varying concentrations of the prodrug, 2-fluoroadenine, 24 hours later. Cell viability was assessed using the alamar blue viability assay. Melanoma



cells that had been transfected with PNP exhibited much lower survival rates upon exposure to the prodrug. A graphic illustration of the results is attached as Exhibit E.

In the fifth set of experiments, B16 melanoma cells were transfected with a nucleic acid encoding cytosine deaminase (CD) in a lipid-nucleic acid complex and exposed to varying concentrations of the prodrug, 5-fluorocytosine, 24 hours later. Cell viability was assessed using the alamar blue viability assay. Melanoma cells that had been transfected with CD exhibited much lower survival rates upon exposure to the prodrug. A graphic illustration of the results is attached as Exhibit F.

These experiments demonstrate that nucleic acids other than those encoding HSV-TK are effective for inhibiting tumor growth when administered at a site distal to the tumor. These experiments also demonstrate that genes other than suicide genes are effective for inhibiting tumor cell growth. In particular, these experiments demonstrate that, administration of fully encapsulated nucleic acids encoding cytokines, tumor suppressor proteins, and cytotoxins are effective in inhibiting tumor growth.

13. It is my understanding that in the Office Action mailed April 10, 2000, the Examiner cited a number of references (Schofield, *et al.*, Crystal, Verma *et al.*, Friedmann, Branch, and Cooper) that allegedly demonstrate that gene therapy is unpredictable and surrounded by significant hurdles. However, a perusal of these references reveals that they actually support the proposition that gene therapy works. In particular, Schofield *et al.* describe liposomal delivery of DNA *in vivo* as "an attractive alternative to viral transfer methods due to [the lack of] DNA size constraints, lower immunogenicity, and easier bulk preparation." Crystal discloses that "plasmid-liposome complexes have many advantages as gene transfer vectors, in that they can be used to transfer expression cassettes of essentially unlimited size, cannot replicate or recombine to form an infectious agent, and may evoke fewer inflammatory or immune responses because they lack proteins." Verma *et al.*, teach that non-viral vectors are useful for "generat[ing] safe and efficient gene delivery system[s]." Friedmann teaches that non-viral vectors can "condense the DNA, deliver it to cells, and protect it from degradation


inside cells." Furthermore, Friedmann teaches that "[g]ene transfer by liposomes ... has advanced enough for these vectors to enter clinical trials for such diseases as cancer and cystic fibrosis." Cooper teaches that "[a] particular advantage of [liposome-mediated gene delivery] is the ease of preparing DNA/liposome complexes, the stability of the individual components, and the versatility to transfect a variety of tumor types." Moreover, Cooper teaches that "[l]iposome/DNA complexes administered intravenously can also deliver plasmid vectors into multiple tissue types."

Branch stands in contrast to the other cited references in that it teaches *antisense* strategies for knocking out gene function. Nucleic acids delivered as described by Branch are intended to cause the destruction of their target and are *not* meant to be expressed. Branch explicitly states that "[t]he purpose of this article is to review the factors that make and break specificity in antisense applications ... [o]nly antisense molecules and ribozymes designed to inhibit RNA targets are considered here." Moreover, there is no hint or suggestion in Branch that the antisense nucleic acids are encapsulated in any vector, viral or non-viral.

Thus, taken together, the cited references support the proposition that gene therapy is effective and that lipid-nucleic acid particles are useful for treating neoplasias.

14. In view of the foregoing, it is my scientific opinion that one of skill in the art would be able to practice the claimed invention with, at most, routine experimentation using the guidance in the specification and what is known to those of skill in the art. The specification, therefore, fully enables the methods of the invention.

15. The Declarant has nothing further to say.

Dated: March 8, 2002 By:   
Ian MacLachlan, Ph.D.

# Curriculum Vitae

**Ian MacLachlan**

#406-272 East 4th Avenue  
Vancouver, British Columbia.  
Canada, V5T-4S2  
Telephone: 604-734-0074  
E-mail: ianm@inexpharm.com

## Education

May 1988 - June 1994	Ph.D. (Biochemistry), University of Alberta, Edmonton, Canada, & Department of Molecular Genetics, University of Vienna, Austria.
September 1985 - May 1988	B.Sc. (Biochemistry) University of Alberta, Edmonton, Canada.
September 1982 - May 1984	Biological Sciences University of Calgary, Calgary, Canada.

## Experience

Sept 2000 – Present Protiva Biotherapeutics, Inc. 150-8900 Glenlyon Parkway Burnaby, B.C.	Chief Scientific Officer Non-viral Gene Transfer
July 1996 – Aug 2000 Inex Pharmaceuticals Corporation 100-8900 Glenlyon Parkway Burnaby, BC	Team Leader / Research Scientist Non-Viral Cancer Gene Therapy Suicide Gene Therapy, Tumor Biology Vector Development, Inducible Gene Expression
July 1994 - June 1996 Howard Hughes Medical Institute University of Michigan Ann Arbor, MI Supervisor: Dr. G.J. Nabel	Research Fellow, Department of Internal Medicine TNF Mediated Activation of NF- $\kappa$ B Adenoviral Gene Therapy for Restenosis Role of NF- $\kappa$ B in Vertebrate Development
May 1988 - June 1994 Lipid and Lipoprotein Research Group University of Alberta & Dept. of Molecular Genetics University of Vienna Supervisor: Dr. Wolfgang Schneider	Ph.D. Thesis Research: Characterization of receptor mediated uptake of riboflavin binding protein including cloning and characterization of the <i>rd</i> mutant.
January - April 1988 University of Alberta Supervisor: Dr. Wayne Anderson	Research: Computerized sequence analysis of lipoproteins, protein crystallography.
September - December 1987 University of Alberta Supervisor: Dr. Wolfgang Schneider	Research: Purification and characterization of apolipoprotein VLDL-II.

Summer 1987  
Bamfield Marine Station, Canada  
Supervisor: Dr. Ron Ydenberg

Research:  
Behavioral analysis of the polychaete,  
*Eudystilia vancouveri*.

May 1983 - December 1986  
Canadian Hunter Exploration Ltd.  
Supervisor: Murray Grigg  
605 5th Ave.  
Calgary, Alberta.

Computer programming of oil and gas reservoir  
simulations and data analysis tools for an  
oil and gas company.

#### **Additional Training**

June - September 1998  
Leadership Edge Consulting

Lab-to-Leader Training Program  
Project Management, Coaching, Team Management

October 1997  
Pape Management Consulting

Project Management Training II

February 1997  
Pape Management Consulting

Project Management Training I

#### **Awards**

1995- 1998

Medical Research Council of Canada Fellowship

1993

Mary Louise Imrie Graduate Award, Faculty of Graduate Studies  
and Research, Vice-President (Research), University of Alberta

1992 - 1994

Austrian Fonds zur Förderung der Wissenschaftlichen Forschung  
(Austrian Ministry of Science Scholarship)

1989 - 1993

Heart and Stroke Foundation of Canada Research Trainee

1982

Rutherford Scholarship

#### **Memberships and Affiliations**

1998 -Present

American Society of Gene Therapy, Member

1999 -Present

Science Council of British Columbia,  
Health Technology Committee Member

#### **Patents Applied For**

Finn, J., MacLachlan, I., Autogene Nucleic Acids Encoding a Secretable RNA Polymerase, Filed 2001.

MacLachlan, I., Graham, R.G., Systemic Delivery of Serum Stable Plasmid Lipid Particles for Cancer  
Therapy, Filed 1998.

MacLachlan, I., Buchkowski, S.S., Sensitizing Cells To Compounds Using Lipid Mediated Gene and  
Compound Delivery, Filed 1998.

Joshi, P.J., Mortimer, I.C., Tam, P., MacLachlan, I., Graham, R.G., Combination Therapy of Nucleic Acids  
and Conventional Drugs, Filed 1998.

## Publications

MacLachlan, I., Tam, P., Lee, D., Thompson, J., Giesbrecht, C., Lee, A., Thompson, V., Graham, R.G., A Gene Specific Increase in the Survival of Tumor Bearing Mice Following Systemic Non-viral Gene Therapy, Submitted.

Buchkowsky, S.S., MacLachlan, I., Graham, R.W., Liposomal Encapsulation of Ganciclovir Results in Improved Pharmacokinetics and Biodistribution, Submitted.

Cullis, P.R., MacLachlan, I., Fenske, D.B., Lipid Based Systems for Systemic Gene Therapy, Journal of Liposome Research, In Press.

Fenske, D.B., MacLachlan, I., Cullis, P.R., Stabilized Plasmid-Lipid Particles: a Systemic Gene Therapy Vector, Methods in Enzymology, Academic Press, San Diego, In Press.

Pampinella, F., Lecheardur, D., Zanetti, E., MacLachlan, I., Benhaouga, M., Lukacs, G.L., Vitiello, L., Analysis of Differential Lipofection Efficiency in Primary Vs Established Myoblasts, Molecular Therapy, 5:161-169, 2002.

Fenske, D.B., MacLachlan, I., Cullis, P.R., Long-circulating Vectors for the Systemic Delivery of Genes, Current Opinion in Molecular Therapeutics, 3 (2):153-158, 2001.

Pampinella, F., Pozzobon, M., Zanetti, E., Gamba, P.G., MacLachlan, I., Cantini, M., Vitiello, L., Gene Transfer In Skeletal Muscle by Systemic Injection of DODAC Lipopolyplexes, Neurological Science, 21:S971-973, 2000.

MacLachlan, I., Cullis, P.R., Graham, R.W., Synthetic Virus Systems for Systemic Gene Therapy. In: *Gene Therapy: Therapeutic Mechanisms and Strategies*, Smyth-Templeton, N., Lasic, D.D., (Eds.) Marcel Dekker, New York, 2000.

MacLachlan, I., Cullis, P.R., Graham, R.G., Progress Towards a Synthetic Virus for Systemic Gene Therapy, Current Opinion in Molecular Therapeutics, 1: 252-249, 1999.

Mortimer, I., Tam, P., MacLachlan, I., Graham, R.W., Saravolac, E.G., Joshi, P.B., Cationic Lipid Mediated Transfection of Cells in Culture Requires Mitotic Activity, Gene Therapy, 6: 403-411, 1999.

Wheeler, J.J., Palmer, L., Ossanlou, M., MacLachlan, I., Graham, R.W., Hope, M.J., Scherrer, P., Cullis, P.R., Stabilized Plasmid Lipid Particles: Construction and Characterization, Gene Therapy, 6: 271-281, 1999.

Wu, B., Woffendin, C., MacLachlan, I., Nabel, G.J., Distinct Domains of I $\kappa$ B- $\alpha$  Inhibit Human Immunodeficiency Virus Type I Replication Through NF- $\kappa$ B and Rev, J. Virology, 71(4):3161-3167, 1997.

MacLachlan, I., Steyrer, E., Hermetter, A., Nimpf, J., Schneider, W. J., Molecular Characterization of Quail Apolipoprotein II: Disulphide-bond Mediated Dimerization is Not Essential For Inhibition of Lipoprotein Lipase. Biochem. J. 317: 599-604, 1996.

Elkin, R.G., MacLachlan, I., Hermann, M., Schneider, W.J., Characterization of the Japanese Quail Oocyte Receptor for Very Low Density Lipoprotein and Vitellogenin, J. Nutrition, 125: 1258 - 1266, 1995.

MacLachlan, I., Nimpf, J., Schneider, W. J., Japanese Quail Apo-VLDL-II: cDNA Sequence and Comparison to Chicken Apo-VLDL-II, a Specific Inhibitor of Lipoprotein Lipase. Atherosclerosis: 109: 62, 1994.

MacLachlan, I., Schneider, W.J., Avian Riboflavin Binding Protein Binds to Lipoprotein Receptors in Association With Vitellogenin. J. Biol. Chem., 269: 24127-24132, 1994.

MacLachlan, I., Nimpf, J., White, H.B. , Schneider, W.J., Riboflavinuria in the *rd* Chicken: 5' -Splice Site Mutation in the Gene for Riboflavin Binding Protein, J. Biol. Chem. 268 : 23222-23226, 1993.

MacLachlan, I., Nimpf, J., Schneider, W.J., A Point Mutation in the Gene for Riboflavin Binding Protein Leads to Activation of Alternate Splicing Pathways Causing Riboflavinuria in the *rd* Chicken. Fed. Amer. Soc. Exper. Biol. Jour., 7: A1091, 1993.

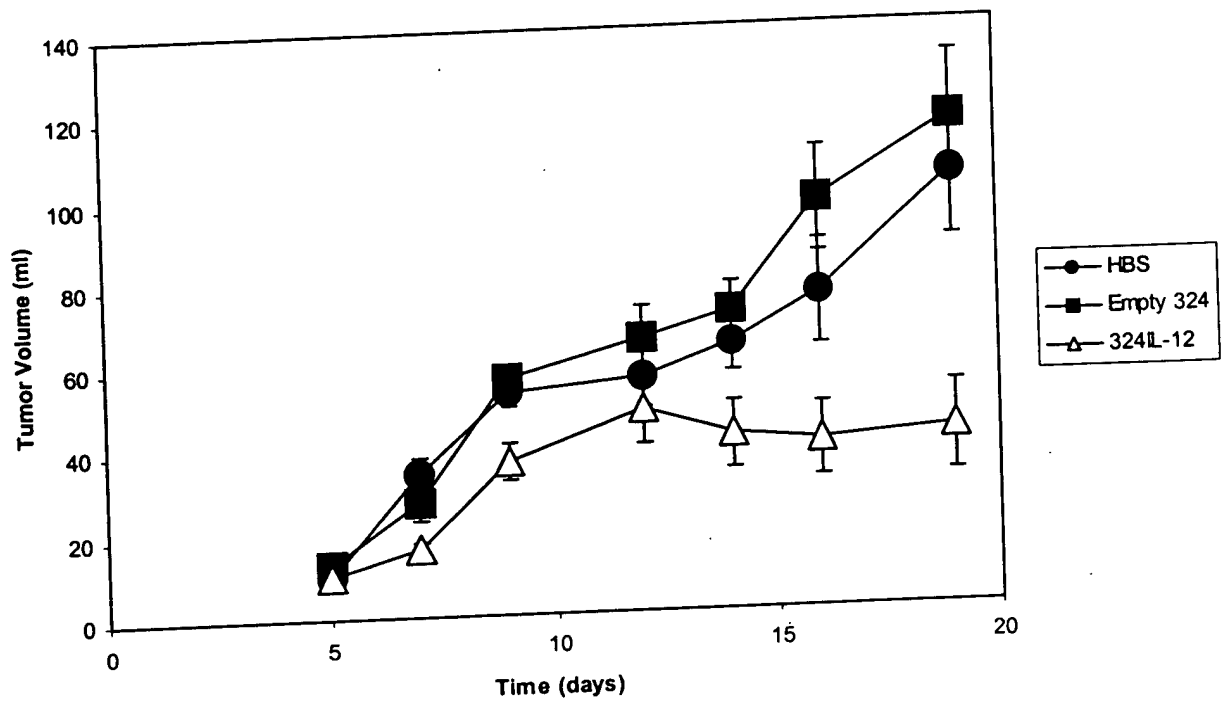
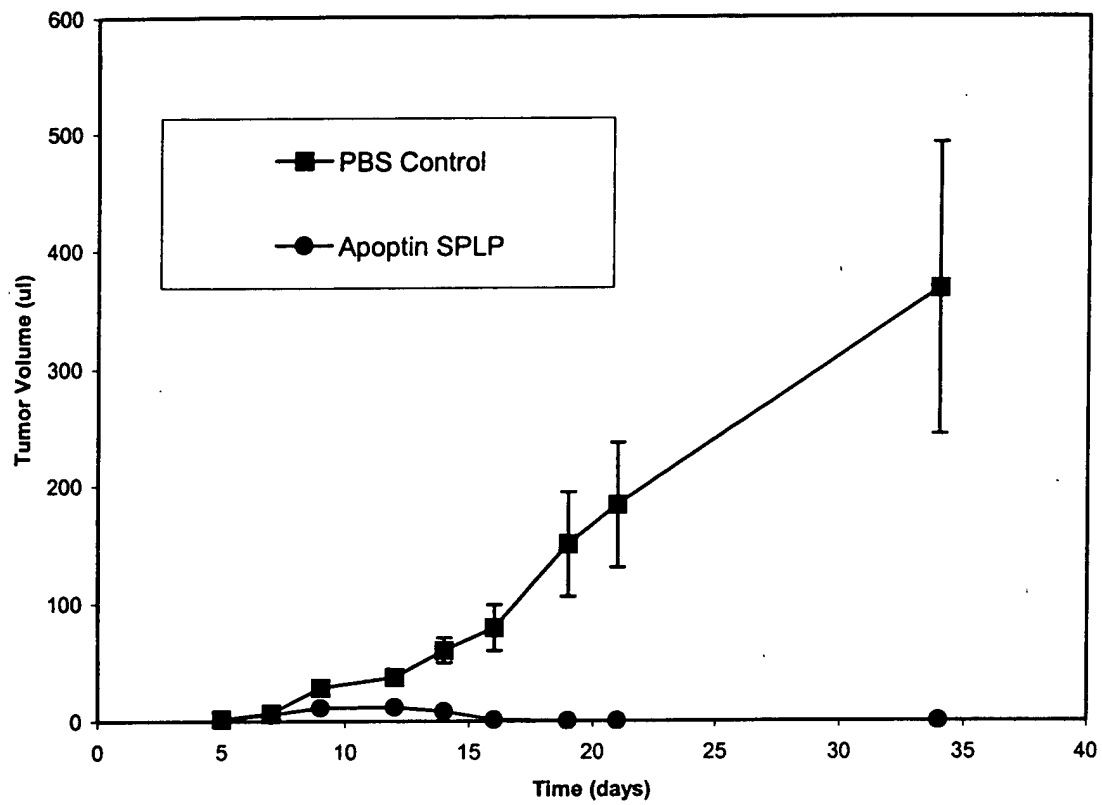
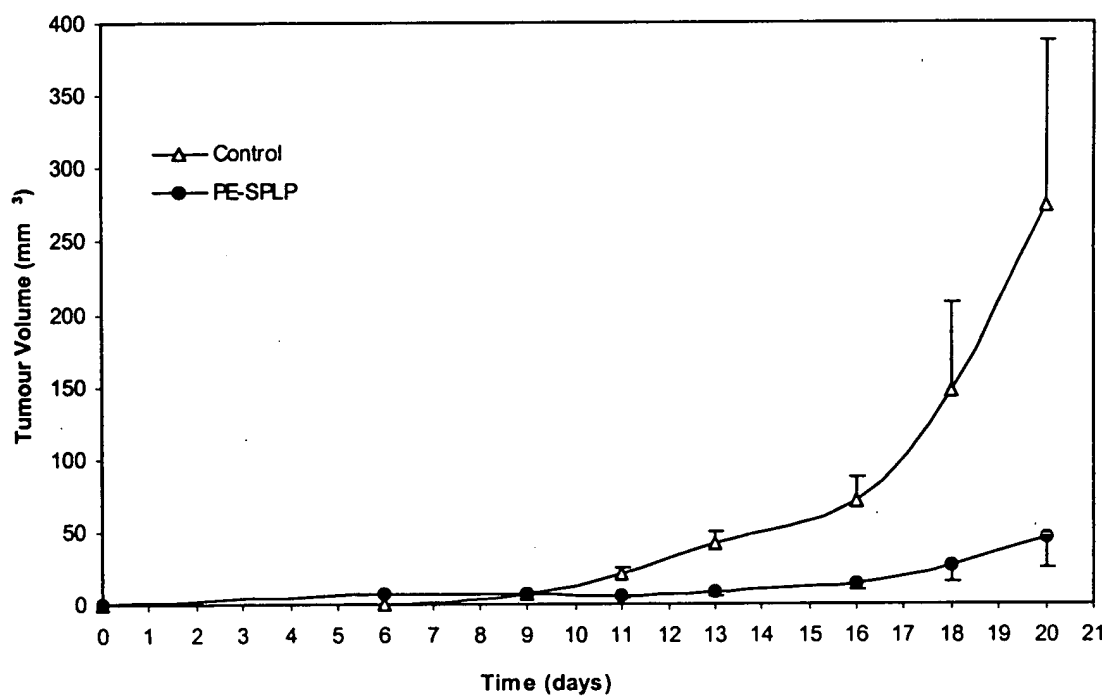


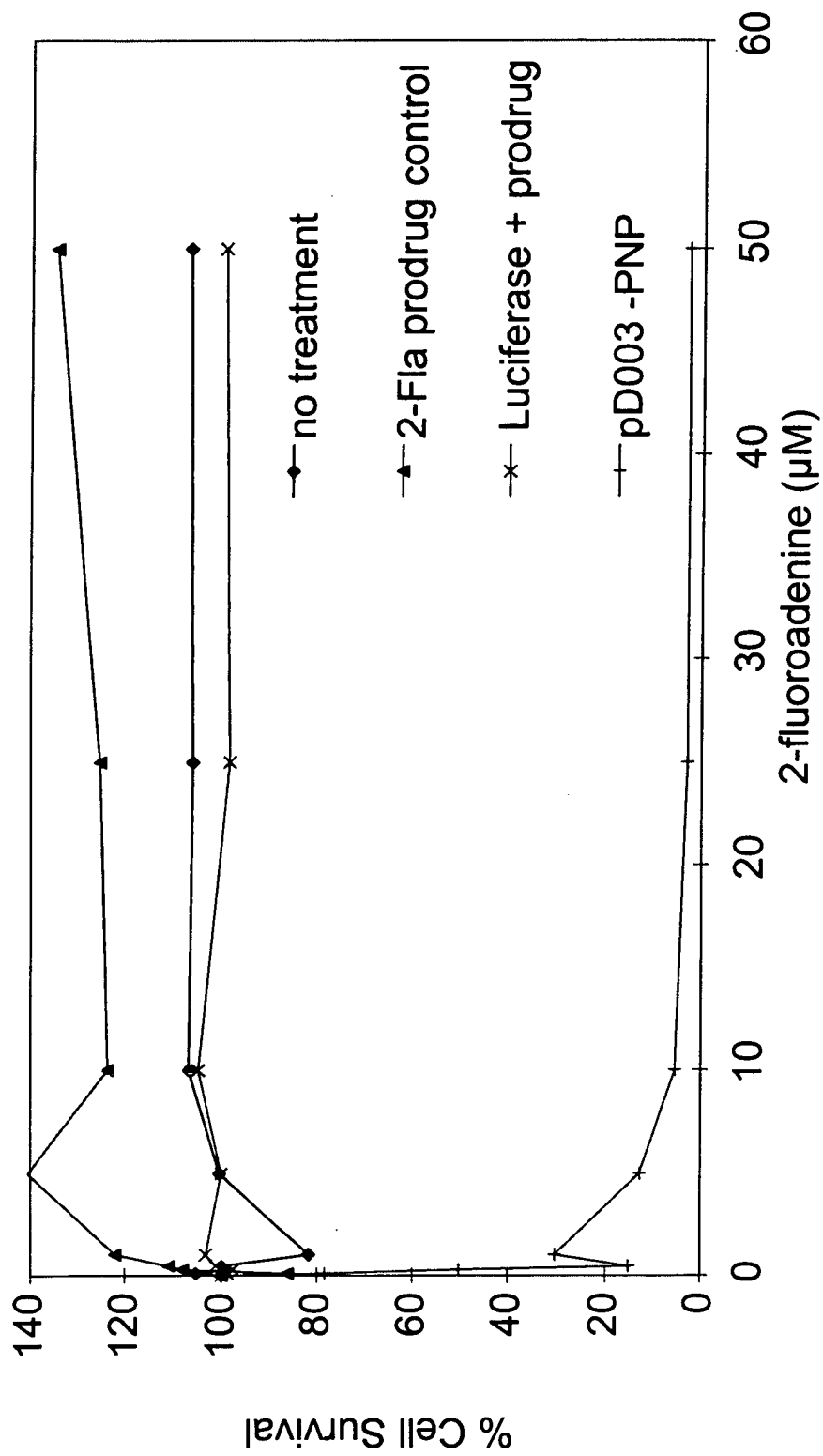
EXHIBIT B







# PNP:2-Fluoroadenine Suicide Gene Therapy



# Cytosine Deaminase Suicide Gene Therapy

